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**FOCAL NECROSIS OF THE ADRENAL GLAND: WITH REMARKS
UPON ACUTE ADRENAL INSUFFICIENCY.**

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INTRODUCTION. The lesion is an unusual one. While it has been reported many times, the descriptions have been meager and often inaccurate. Indeed, I have been unable to find a single graphic representation of this lesion in the literature. Moreover, it has never been described as a distinct and unalloyed lesion of the adrenal, and, in consequence, has thus far been nameless. The name I have suggested fits the morphological characteristics accurately; indeed, the resemblance to the more familiar focal necroses of the liver is a very close one. These facts, it seems to me, warrant the purpose of this study, which is based upon two cases observed within a short time.

The study of these two cases led inevitably to an examination of the clinical features of acute adrenal insufficiency, a phase that is always associated, and, moreover, is paramount in nearly all the contributions to the study of this lesion. The reports are so diverse and confusing that it seemed wise at the same time to submit a critique of this aspect as well.

CASE I.—H. B., aged forty-one years, male. Admitted October 26, 1913. Three weeks before admission the patient complained of headache, distress in the epigastrium and in the precordium, weakness and anorexia. He had relief for a few days, then the symptoms returned, especially the intense headache. Patient was

dizzy, had flashes before his eyes and there was puffing of forehead and face. The urine showed a trace of albumin and gave a positive test with the guaiac reaction. Roentgen-ray report on October 27, 1913, shows a calculus in the left kidney.

Operation, November 10. Right nephrectomy by Dr. Goodman. Pathological report: Calculous pyelonephritis. Patient was returned to bed in profound shock; pulse, 146. Intravenous infusion given.

November 11. Pulse, 112, poor in quality; temperature, 96 to 97.4°; respiration, 14.

November 12. 8 A.M., pulse, 80; respiration, 16. 12 M., temperature, 93.6°; respiration, 8. 6 P.M., temperature, 93.6°; respiration, 10. 9 P.M., temperature, 96°; respiration, 20. 11 P.M., temperature, 96; respiration, 20.

November 13. Ceased to breathe.

Report on Removed Kidney. The kidney is about twice the normal size; granular surface; capsule not adherent. The pelvis is enormously dilated and congested. It is coated with exudate in many areas and contains bloody purulent urine and one large free stone. The parenchyma of the kidney is pale red; markings poor; cut surface markedly granular; papillæ much flattened.

Microscopically. There is an abundant growth of new connective tissue between the tubules in all stages of organization. The tubules are dilated; the epithelium is flat, granular and stains poorly. Many of the tubules contain hyaline cylinders and fresh blood, especially in the straight papillæ. The glomeruli are fairly well preserved, somewhat contracted; within many of the capsules is a fine granular material. The lining squamous epithelium of the pelvis is well preserved; here and there it is covered by fresh exudate. There is a notable increase of the round cells beneath the epithelium. Diagnosis: calculous pyelonephritis.

Autopsy. Lungs, heart and right adrenal not removed.

Left Kidney. About twice normal size. Surface smooth; dark brownish red. There are numerous punctate, hemorrhagic spots the size of a pinhead. On section, deeply congested; cortex thickened; markings clear; glomeruli easily visible.

Spleen. Normal.

Pancreas. Normal.

Aorta. Moderate atheroma.

Adrenal. Very large, distinct capsule, white center, surrounded by hemorrhagic fat.

Anatomical Diagnosis. Compensatory hypertrophy of kidney, with acute congestion.

Microscopic Examination. *Kidney.* Hemorrhages in tubules; slight edema of stroma; moderate parenchymatous nephritis.

Spleen. Normal.

Pancreas. Normal.

Aorta. Small amount of lime in media.

Adrenal (Fig. 1). Larger than normal and embedded in hemorrhagic tissue.

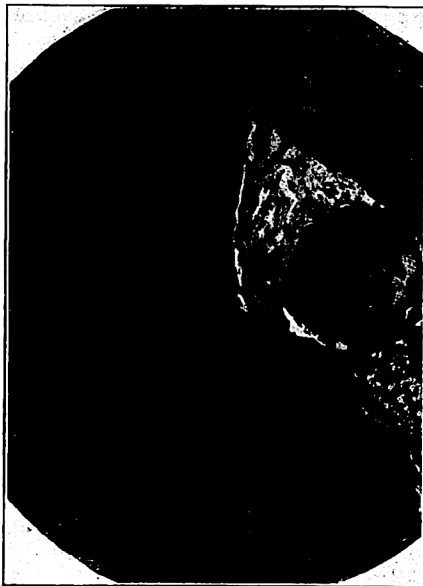


FIG. 1.—Low-power appearance of adrenal from Case I, showing a number of areas of focal necrosis in the cortex and thrombi in the capsular vessels.

With the low power there are perhaps a dozen or more foci where the normal parenchyma of the organ has been manifestly destroyed. These areas are distinctly circumscribed from the surrounding parenchyma and take little or no hematoxylin stain. The majority of these foci have a hemorrhagic appearance, due to the presence of masses of red blood cells. These foci are uniformly round; some are confluent and exist exclusively in the cortex. The medulla is intact. As a rule there is a thin rim of cortex between the foci and the surface of the organ, although some extend to the very surface itself. The majority of these foci have a honey-combed appearance, due to the presence of well-preserved strands of intertrabecular connective tissue.

Upon studying these foci with the high objective (Fig. 2) we find the adrenal tissue has been almost completely destroyed; that

parenchyma cells are mere "shadows" without nuclei or very pale ones. They have entirely lost their normal arrangement and stain deeply with eosin. In some foci no trace of parenchyma whatever is visible, being replaced by a pale acellular tissue resembling fat. Scattered throughout these foci are abundant polymorphonuclear cells. In some foci these are so abundant as to almost warrant the term abscess. The polymorphonuclear cells are distributed evenly throughout the foci; in some, and especially those that reveal the

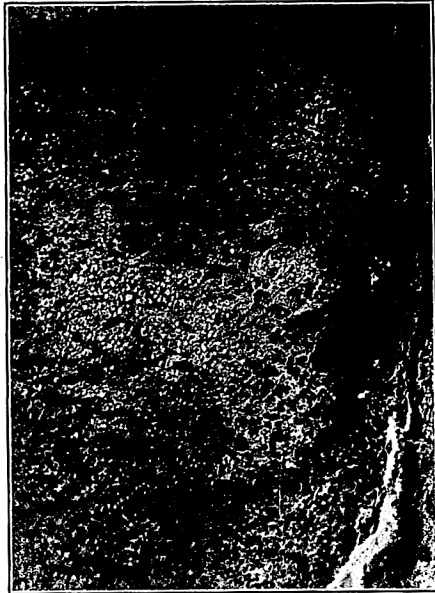


FIG. 2.—High power of one of the focal necroses, showing intense parenchymatous degeneration and peripheral polymorphonuclear infiltration.

most profound necrosis, the polymorphonuclear cells are densely arranged around the circumference of the focus. These foci also contain abundant red cells. These cells are sometimes distributed haphazardly, as in a hemorrhage. In some areas they are present within dilated capillaries. In addition to these three cellular elements—namely, destroyed parenchymatous cells, polymorphonuclear leukocytes and red blood cells—we find in these foci a fourth element—namely, radially arranged strands of the intertrabecular connective tissue—which give the honey-combed appear-

ance described above. These strands are especially abundant near the periphery of the foci, becoming absent in the central portions.

The parenchyma of the organ between and surroundings these foci are very well preserved. There is some engorgement of the cortical capillaries, and in the medulla a few of the veins are filled with a red thrombus.

The connective-tissue capsule of the adrenal is normal.

The fatty and connective tissue immediately surrounding the organ, however, is intensely hemorrhagic. Especially noteworthy is the uniform presence of hemorrhagic and mixed thrombi in the vessels. The vessels appear greatly dilated and are either completely or nearly completely filled with thrombus consisting of fibrin, with a greater or lesser admixture of red blood cells. The intima is completely absent wherever the thrombus is in contact with the wall of the vessel, but there is nowhere evidence of beginning organization.

Summary. A man, aged forty-one years, with calculous pyelonephritis. Nephrectomy was done. Promptly after the operation the patient went into profound shock. After an intravenous infusion he rallied so that on the following day his pulse was 112, although firm in quality. For the remaining two days of his life his temperatures were subnormal, 93.6° to 96° F., with normal pulse rate and decreased frequency of respiration.

CASE II.¹—Jennie G., aged eight years, was admitted to the Beth Israel Hospital January 1, 1916. Her parents and their four other children were alive and well.

The child had been nursed until one year of age. She had suffered from a chronic cough from the eleventh month until the end of the second year, when she had a severe attack of measles. During the fourth year it was noticed that the child's abdomen became enormously enlarged and that she steadily lost weight. At that time Dr. Hymanson suspected tuberculous peritonitis, although the temperature was normal and the von Pirquet test was negative. The parents would not permit tapping of the abdomen. On prolonged use of tonics, with creosote, together with good nourishment, the child gained weight, and in the course of eighteen months the ascites almost disappeared.

In the month of May, 1914, the child was brought to Dr. Hymanson and the mother told him that for the previous two months the patient had again been losing weight; had had frequent micturition, with milky urine. The child was very anemic, weighed only twenty-eight pounds and some dulness could be detected at the lower part of the abdomen. The urine looked turbid and fibrinous coagula were observed when it stood for some time. By shaking the urine with ether the dissolved fat rose to the surface and the

¹ For the details of the clinical history I am indebted to Dr. Hymanson.

urine became quite clear. Microscopically the fat globules were in a fine state of subdivision. Sudan III stained the fat particles red. No filaria and no blood had been detected. By advising complete rest, involving absence from school, and the administration of salol, urotropin and belladonna there was slow improvement; some weight was gained, and on July 31, 1915, the urine was examined by Dr. Max Kahn, who reported that it contained a huge amount of mucin, but no lactose, fat or casein.

November 27, 1915, the frequent micturition and milky urine reappeared. Dr. D. Constantinides examined the urine and found albumin, 0.365 per cent.; fat, 0.225 per cent.; also some pus cells and epithelium; no sugar. On allowing the urine to stand a cream-like mass of fat rose to the surface.

Condition on Admission. The child was anemic and very emaciated, weighed only thirty-four pounds, was not playful, complained of frequent frontal headache, was nauseated and vomited several times a day. The heart, lungs and abdominal organs were normal; there was some dullness at the lower part of the abdomen and some nodules could be palpated at the right inguinal region. The glands in both groins were also palpable. There was no edema and no cyanosis. The patellar reflexes were somewhat exaggerated. Temperature, 99.4°; pulse, 120; respiration, 28.

A blood examination showed erythrocytes, 3,800,000; total leukocytes, 14,400; polymorphonuclear cells, 70 per cent.; lymphocytes, 30 per cent. There was no eosinophilia. The hemoglobin was 60 per cent. No filaria were found in the blood.

Von Pirquet tests were done twice, with negative results. Wassermann test was also negative. The stools contained no ova or red cells. The guaiac test for sugar was positive.

The urine also contained lecithin and cholesterolin.

The microscopic examination of the urine showed many white cells, a few hyaline casts and bladder epithelia, but no filaria. A diagnosis of chyluria was made.

During the first week of the child's stay in the hospital, under the administration of urotropin and sodium benzoate, her condition improved somewhat and at times the urine almost cleared up, but it always contained some fat. Then the temperature began to rise and reached as high as 104.6°. The headache, nausea and anorexia increased in severity, the urine became loaded with pus, was markedly ammoniacal and the fat was increased in quantity. The stools contained some blood. The cervical glands became enlarged, although there was no congestion of the throat, and some ecchymotic spots were noticed all over the body and extremities. The pulse became very weak and at times irregular.

The eyes were examined by Dr. Ervin Török on January 15, who found that the pupils reacted only sluggishly to light. Both disks were covered with a whitish exudate and were moderately swollen.

There were several hemorrhages on and around the disks. The bloodvessels were large and tortuous. Diagnosis: albuminuric retinitis.

A blood culture was negative. The same evening and on the following day the patient had a number of convulsive attacks, which were most marked on the right side of the body. These were controlled by chloroform. A lumbar puncture was done, but the spinal fluid was normal.

On January 17 the patient became comatose and the pulse was at times imperceptible. The cervical glands became more enlarged and death ensued from cardiac failure.

Necropsy. A necropsy was performed on the child eight hours after death. The body was very much emaciated. The cervical, axillary and groin glands were enlarged. Some ecchymotic and petechial spots were noticed over the extremities. The *lungs* were normal except for some slight congestion at the bases. The *heart* was much enlarged, the muscle of the left ventricle being about 2.5 cm. thick, firm and pale. The left ventricle was dilated; the muscle of the right ventricle was 1 cm. thick. The valves were normal, with the exception of a few atheromatous patches on the ventricular surface of the mitral valve. The *liver* was slightly enlarged, and on section was pale, brownish red and cloudy. The *stomach* mucosa was covered with mucus, but otherwise normal. The *right kidney* was 8 x 3 x 2 cm. It was very irregular in contour, showed fetal lobulations, and was fairly firm, with adherent capsule. The surface beneath was very irregular, with numerous depressions and sulci between prominences representing remnants of kidney tissue. These prominences were paler than the surrounding portions, project above the surface, and, on section, were grayish and sharply defined from the surrounding tissue. Section through the kidney proper showed a complete obliteration of all markings, so that it was impossible to differentiate cortex from medulla. The cut section was pale red. There were numerous ecchymoses on the surface, the pelvis was somewhat dilated and the papillæ were flattened. The ureters were somewhat dilated and thickened. The left kidney was 6 x 3 x 2 cm., was somewhat smaller than the right and presented practically the same picture, except for the absence of fetal lobulations. Only the left *adrenal* was removed: it was slightly enlarged, otherwise normal. The *pancreas* was enlarged. The *spleen* was enlarged and measured 12.5 x 6 x 3 cm. The surface was smooth; it was deep red on section and the pulp was firm. Malpighian bodies were prominent. There was a fresh infarct of a dirty brown color, about the size of a bean, in the lower pole, soft in texture and sharply circumscribed from surrounding tissue. The *intestines* were normal. The *mesenteric lymph* nodes were enlarged. The *bladder* was dilated, the walls being extremely hypertrophied; the mucosa was smooth and presented many ecchymotic areas.

Anatomical Diagnosis. Chyluria; chronic diffuse nephritis (contracted kidney); chronic congestion of lungs; hypertrophy and dilatation of the left ventricle; splenic hyperplasia, with fresh infarct; parenchymatous degeneration of the liver; hypertrophy and dilatation of the bladder; hypertrophy and dilatation of ureters.

Microscopic Examination. Lungs. The epithelium of the bronchi was desquamated and the lumen contained an exudate of polymorphonuclear cells. Around the smaller bronchi the alveoli contained an exudate consisting of polymorphonuclears and round cells. The walls of the alveoli in the remainder of the lung were thickened and the capillaries were markedly dilated. The muscular fibers of the heart were normal and there was no infiltration. The cells of the liver were slightly granular and the nuclei somewhat pale. There was a very moderate amount of fat in the cells.

Spleen. The splenic veins were dilated and filled with blood. The infarct showed profound necrosis, with many "shadow" cells and nuclear detritus. Some of the bloodvessels in the necrosed area were still preserved and contained red thrombi; other vessels showed beginning hyaline degeneration. The splenic veins surrounding the infarct were dilated to an enormous size. The capsule and trabeculae of the spleen were normal.

The pancreas showed a few areas of autodigestion. Scattered here and there throughout the organ were small focal areas of polymorphonuclear infiltrations. In these areas the pancreatic cells stained less deeply than in the remainder of the organ. The islands of Langerhans were normal.

Kidneys. The microscopic picture of the kidneys, even on superficial inspection, showed complete disorganization. The interstitial connective tissue was enormously increased and in areas showed a profound infiltration, with round and plasma cells. The tubules varied greatly in size and in shape; no distinction could be made between any of the various portions of the tubules. The majority of the tubules were dilated and the epithelium was flat and stained poorly. Most of them contain hyaline casts and some of these casts contained polymorphonuclear cells. The glomeruli revealed various forms, some being completely hyaline, some partially so; some contained new connective tissue, others were enormously hypertrophied and others showed a polymorphonuclear infiltration. The Bowman capsules were uniformly intact. A few of the glomeruli contained bacterial thrombi. The capillaries were very prominent and dilated.

The intestines and the mesenteric lymph nodes were normal. In the submucous connective tissue of the bladder there was a marked blood extravasation, but the organ was otherwise normal.

Adrenal (Fig. 3). With the low power the most striking feature is the presence of numerous plugs of bacteria situated immediately beneath the connective-tissue capsule of the adrenal or slightly

beneath it. These plugs are dense and are either perfectly round or sausage-shaped, obviously conforming to the lumen of the capillary in which they are plugged. These plugs exist singly or in groups of two or more, and are usually surrounded by a comparatively small number of polymorphonuclear leukocytes. Many plugs, however, are not surrounded by any reactive zone of leukocytes whatever. On the other hand, we find numerous focal, small collections of leukocytes in which no bacterial plugs can be demon-



FIG. 3.—Section from adrenal Case II, showing bacterial infarct in cortex with slight polymorphonuclear infiltration.

strated (Fig. 4). Some of these focal collections of leukocytes surround a small area of necrotic adrenal tissue, as evidenced by "shadow cells," as in the previous case. The polymorphonuclear infiltration affects the intertrabecular connective tissue.

The capillaries of the adrenal are engorged and here and there is a small ecchymosis. With the exception of a lighter stain than normal the parenchyma of the adrenal is normal.

The connective tissue surrounding the organ shows considerable extravasation of blood. The vessels show no change whatever.

Incidence of Focal Necrosis of the Adrenal. In an examination of many hundreds of adrenals, these are the only two that have shown definite evidence of an inflammatory lesion. My autopsy experience in infectious diseases, it must be confessed, has been rather limited.

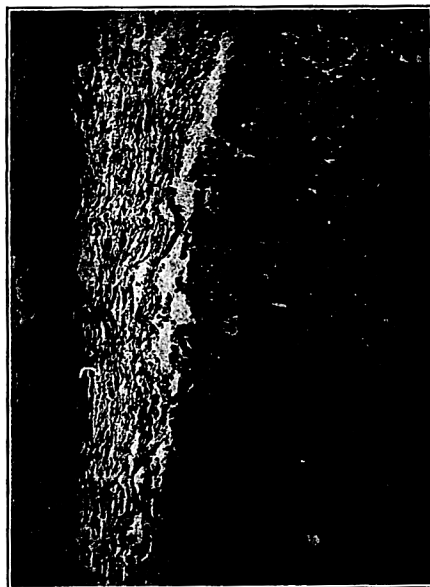


FIG. 4.—Section from adrenal Case II, showing bacterial infarcts in cortex, with practically no polymorphonuclear infiltration.

A study of the literature, on the other hand, confers the impression that inflammatory changes in the adrenal of human beings are not uncommon, although the data are too few to gauge the precise incidence. Babes² in a series of 150 consecutive autopsies found acute lesions of the adrenal in 25 cases. In 11 there was hyperemia, with disappearance of fat, sometimes associated with small hemorrhages in the gland and infiltration of the capsule. In these cases one finds foci of polymorphonuclears or mononuclears, with degeneration or necrosis of the parenchyma. In 14 cases of infectious disease Babes found foci of bacteria in the cortex unas-

² Compt. rend. Soc. de biol., 1908, lxx, 235.

sociated with secondary inflammatory reaction. Marchetti,³ in a series of 1200 autopsies, describes congestion and hemorrhage of the adrenals in the infectious diseases. Goldschmidt,⁴ in a study of 53 adrenals in all kinds of diseases, found lymphocytic infiltration in infectious diseases and evidences of phagocytosis in the cortex cells resembling in appearance the 'Russel bodies' found in malignant tumors. Ziegler⁵ says that small foci of inflammation may occur in the infectious diseases which may pass into suppuration and subsequent scar formation. Aschoff⁶ describes edema of the adrenal in infectious diseases as common. Rarer are embolic foci in the cortical zone resulting in "herdförmige" acute inflammations. From these, he says, miliary or even larger abscesses may form. Scheel⁷ describes edema of the interstitial tissue of the adrenals as a frequent occurrence in febrile disorders. Neusser and Wiesel⁸ say that acute inflammations of the adrenals are not rare; these occur most often in the form of edema and parenchymatous degenerations. He describes focal necroses as occurring in severe infections, especially in diphtheria. Loeper and Oppenheim⁹ noted very small leukocytic infiltrations in bronchopneumonia of children, and in streptococcus infections. These same authors¹⁰ have found inflammatory lesions in diphtheria, variola, typhoid and tetanus. They mostly found parenchymatous changes. Focal necroses they noted only in diphtheria. In other diseases, areas of necroses are found, but these are not the direct result of the toxin but are due to hemorrhages. Occasionally they found polymorphonuclear infiltrations of the adrenal. Oppenheim¹¹ describes cases of dysentery in which, at autopsy, the adrenals were large and congested, with cellular necroses and hemorrhages. Beitzke¹² finds bacterial emboli in the adrenal frequently; often this lesion is the only site of bacterial embolism found at autopsy.

Experimental Acute Inflammatory Lesions of the Adrenal. Much work has been done, especially by the French school, to obtain lesions of the adrenals in animals by the injection of pathogenic bacteria. As far back as 1889 Roux and Yersin¹³ found degeneration of the adrenal in experiments in diphtheria. Langlois and Charrin¹⁴ found congestion and hemorrhages in the adrenal after pyocyaneus infections. The most comprehensive experimental

³ Virchows Arch. f. path. Anat., 1904, clxxvii, 227.

⁴ Deutsch. Arch. f. klin. Med., 1909-1910, lxxxxviii, 186.

⁵ Specielle Pathologie, Jena, 1906, 11te Aufl.

⁶ Ibid., Jena, 1912, 2te Aufl.

⁷ Virchows Arch. f. path. Anat., 1908, clxxxvii, 494.

⁸ Erkrankungen der Nebennieren, Leipzig, 1910, 2te Aufl.

⁹ Manuel des Maladies des Rein, edited by Debove, Archard and Castaigne.

¹⁰ Loeper and Oppenheim: Arch. de expér. et d'anat. path., 1901, xiii, 683.

¹¹ Bull. et mém. Soc. méd. d. hôp. de Paris, 1915, xxxix, 1155.

¹² Berl. klin. Wehnschr., 1909, xli, 2, 769.

¹³ Ann. de l'Inst. Pasteur, 1888, ii, 629; 1889, iii, 273.

¹⁴ Compt. rend. Soc. de biol., 1893, p. 812.

studies are those of Oppenheim and Loeper,¹⁵ who obtained lesions in diphtheria, tetanus, anthrax, and pneumococcus infections. They describe hemorrhages, infiltration with leukocytes, parenchymatous degenerations and necrotic foci; the latter are especially characteristic in diphtheria infections. They found the lesions most often in the reticular and fascicular zones of the gland. Labsin¹⁶ found degenerations and hemorrhages of the adrenals in rabbits and in dogs after injection of streptococci. Crowe and Wislocki¹⁷ found necrotic foci in the adrenal cortex of animals after acute general infections.

These observations upon human beings and animals indicate that inflammatory lesions of the adrenals are not uncommon in the infectious diseases. It would seem that they occur more frequently in experimental bacterial infections than in human beings. Also that such lesions are more common and more profound in diphtheria than in any other infection.

Varieties of Lesions of Adrenals Associated with Infections. As we have seen the lesions of the adrenal associated with infections are various. They may be grouped in the following manner: (1) Parenchymatous degenerations; (2) edema of the interstitial connective tissue; (3) hemorrhages; (4) infiltration with leukocytes; (5) focal necroses; (6) bacterial emboli, with or without secondary inflammatory reaction; (7) miliary or larger abscess. Of these the most common are parenchymatous degenerations and hemorrhages. While some writers, especially those that have written textbooks (Ziegler, Aschoff, Kauffmann, and Beneke¹⁸) speak of abscesses of the adrenal as not a strange phenomenon, I have been able to find but 3 authentic cases, those of Chvostek,¹⁹ Janowski,²⁰ and Stursberg.²¹ A curious observation is that made both by Beitzke and Simmonds,²² who found cortical bacterial emboli associated, with parenchymatous degeneration, as the only evidence of bacterial embolism as part of a general infection in the body.

Pathogenesis. So far as available data permits us to judge the lesions in the adrenals may result either from a general toxic action (degenerations, hemorrhages, necroses) or from the action of bacteria themselves (bacterial emboli, abscesses). It seems curious that I have been able to find but few cases of an inflammatory lesion occurring in the medulla of the organ. The lesions that I have described seem to occur mostly in the cortex. Crowe and Wislocki confirmed this observation in their extensive experiments upon

¹⁵ Arch. de méd. expér. et d'anat. path., 1901, xiii, 332.

¹⁶ Arch. de soc. biol. de Petrograd, 1905, xi, 319.

¹⁷ Beitr. z. klin. Chir., 1914, xcv, 8.

¹⁸ Zülzer's Klin. Hand. der Harn. u. sexual organs, Leipzig, 1894.

¹⁹ Wien. med. Presse, 1880, p. 1425.

²⁰ Gaz. lek., 1898, liv, 354.

²¹ Deutsch. med. Wchnschr., 1904, xxx, 1406.

²² Virchow's Arch. f. path. Anat., 1898, clxxii.

acute and chronic infections in animals. The only explanation of this phenomenon I can offer is the peculiar blood supply of the adrenal gland. According to Henle, numerous small arteries from the periphery penetrate into the fibrous capsule of the gland, where they form an anastomosing plexus. These small arteries then penetrate the parenchymal cortex and immediately form capillaries between the cortical columns. From here the blood is collected into small veins in the medulla, whence the blood passes into the adrenal vein. We thus see that bacterial emboli, no matter how small, are promptly caught in the cortical capillaries and have little or no chance to penetrate into the medulla.

If this explanation is valid, the pathogenesis of inflammatory lesions of the adrenal as due to the direct action of bacteria seems the more probable one.

The lesion in my second case is an exquisite example of bacterial embolism.

The lesion in my first case requires a different interpretation. Three explanations are possible:

1. That the lesion was the result of the contagious infection—namely, the pyelonephritis. I do not believe this etiology is probable and for the following reasons: (1) Because it is hard to conceive how an infection of such low grade could cause such an intensely acute lesion. Indeed, so far as I am aware, a focal necrosis in the adrenal has never been observed, either at autopsy or experimentally, in chronic infections. (2) The patient did not reveal any evidence of any grade of general sepsis, either bacterial or toxic.

2. The second explanation is that the lesion may have been due to a postoperation sepsis. Against this explanation is the fact that the patient revealed not the slightest sign of clinical sepsis after the operation.

3. The third explanation, and the one I believe most probable, is that the lesion was due to the peri-adrenal hemorrhage, with consequent thrombosis of the adrenal vessels. My reasons for this belief are: (1) by exclusion of any other factor, and (2) detailed examination of my specimens reveals the fact that the necroses are most abundant in those portions of the adrenals in which the thrombosis of the capsular vessels is most widespread and are correspondingly absent in those portions in which thromboses are absent.

According to this conception the focal necroses in the adrenal may be regarded as infarcts.

Clinical Aspects of Acute Adrenal Insufficiency. The attempt to interpret certain symptoms and signs as due to the obvious interference of function produced by the lesions that I have described is certainly a reasonable endeavor. The French also have been especially active in this field, notably Arnaud, Sergent and Oppen-

heim. Arnaud's²³ contribution appears to have been the first in which a systematic attempt was made to set forth the clinical features of acute adrenal insufficiency, and is based on a study of 80 cases in which hemorrhages, from whatever cause, were found in the adrenals at postmortem examination. Significantly enough, in the vast majority of cases no symptoms that could be directly attributed to the adrenal lesion were present. In 5 cases a hematoma of palpable size was present. In 6 cases the symptoms resembled those of an acute peritonitis. In 8 cases symptoms of so-called "adrenal insufficiency," such as muscular asthenia, prostration, vomiting, diarrhea, abdominal pain, hypothermia, syncope and collapse were present. In 15 cases there was sudden death, or death within a few hours, with symptoms of delirium, convulsions, contractures, coma, hypothermia, syncope, etc. Sergent,²⁴ who has written extensively on the subject, claims to have discovered a pathognomonic sign of acute adrenal insufficiency in the so-called "white line." This sign is obtained by running the finger-nail or pin along the skin, when a white instead of the usual red line will form. This line is supposed to be due to a temporary constriction of the relaxed vessels. He claims that the triad, "white line," hypothermia and asthenia make the diagnosis of acute adrenal insufficiency certain.

Oppenheim describes cases of dysentery in which there was sudden cholera, like collapse, with hypothermia, concave abdomen, small rapid pulse, vomiting and diarrhea. In some instances he obtained the "white line" of Sergent. At autopsy the adrenals were large and congested, and contained cellular necroses and hemorrhages. Good results were obtained by opotherapy.

Dudgeon,²⁵ in an extensive study of acute adrenal hemorrhages, admits Arnaud's classification and adds two syndromata of his own: (1) cases suggesting an acute specific fever, and (2) cases with severe skin lesions, such as purpura.

Lavenson²⁶ reports the case of a woman, aged forty-four years, who suffered from vomiting, epigastric pain, prostration and delirium. The temperature was 98° and the pulse 48 and imperceptible. There was tenderness in the epigastrium and loins. The predominating symptoms were those of shock. She died thirty-six hours after the onset of the illness. At the autopsy there was an acute pancreatitis. There was thrombosis of the adrenal vein secondary to this lesion. The adrenals were enlarged, soft and red, with necroses of the parenchyma and hemorrhagic extravasations. He believes that the symptoms from which the patient suffered were in part due to the adrenal lesion and classifies the

²³ Arch. gén. de méd., 1900, clxxvi, 5.

²⁴ L'Insuffisance surrénale, Paris, 1902.

²⁵ Am. Jour. Med. Sc., 1904, cxvii, 134.

²⁶ Arch. Int. Med., 1908, ii, 62.

recorded cases into the following five types: (1) the asthenic form; (2) cases in which symptoms of shock are present, associated with gastro-intestinal symptoms, bradycardia, lumbar pains and death; (3) cases of sudden death; (4) nervous type, with convulsions, coma and delirium; (5) cases associated with purpuric lesions within the abdominal cavity.

Riesman,²⁷ basing his observations upon Lavenson's report, reports 5 cases of "adrenal insufficiency." The main symptoms were physical weakness amounting to actual prostration, a feeling of coldness, subnormal temperature, slow pulse and low blood-pressure. As all the patients recovered there were no postmortems.

Williams²⁸ describes cases of neurasthenia or psychasthenia with such symptoms as weakness, low blood-pressure and pigmentation of the mucous membranes. Some die and others recover under opotherapy. He believes that some of these cases may arise after periods of hyperfunction of the adrenals due to mental strain (Cannon).

It cannot be said that the protean and conflicting observations thus far adduced afford a sense of satisfaction, as indices of an acute adrenal insufficiency. Indeed, these form adequate grounds for a critique from many aspects.

In the first place we must remember that the presence of a lesion in an organ, even of such profound physiological import as the adrenal, does not necessarily signify that the lesion gives rise to clinical symptoms. For instance, we know that profound degenerations and almost complete destruction of these organs by metastatic tumors may occur without the slightest evidences of Addison's disease (Kaufmann²⁹). Specially significant in this connection are the observations of Arnaud, which we have already quoted, who found that out of 80 cases of adrenal hemorrhage studied, in 46 no symptoms had been present. Obviously the absence of clinical symptoms in cases in which a profound lesion of the adrenal is found at autopsy may be explained in one of two ways: (1) that in many such cases the lesion is unilateral, so that the remaining adrenal assumes the entire physiological function; (2) in cases in which both adrenals are affected, detached portions of unaffected adrenal tissue may be present in the neighborhood or distant parts of the body (*e. g.*, broad ligament, spermatic cord). In any event the absence of symptoms where lesions of the adrenals are present is sufficiently common to make hazardous a clinical deduction based upon pathological findings.

In the second place the function of the adrenal gland is a complex one. The adrenal gland, physiologically speaking, cannot be regarded as a single organ with a single function. Rather it must

²⁷ Jour. Am. Med. Assn., 1912, lviii, 1846.

²⁸ Ibid., 1914, lxi, 2, 2203.

²⁹ Lehrbuch der path. Anat., Berlin, 1911, 6th Aufl.

be regarded as a dual organ, consisting of a medulla and a cortex, each of different embryological origin and each possessing different physiological functions. So far as the physiology of the adrenal has been worked out the cortex functionates to neutralize toxins, bears an obscure relation to the formation of pigment and to the development of some of the secondary sexual characteristics. The medulla, on the other hand, maintains the vascular tone by the elaboration of adrenalin and bears some relation to sugar metabolism. If any of these functions are diminished or absent we could not logically diagnose disease of the whole gland but only of a portion. When we consider, furthermore, that these functions are dependent to a greater or lesser degree upon the activities of other endocrine organs, notably the islands of Langerhans, the thyroid and the pituitary, we can readily understand how difficult it is to create a more or less precise symptom-complex from a disorder of the adrenal function. Certainly the various forms of symptoms-complex that we have quoted bear little relation to the physiology of the organ as we have outlined it. Even in Addison's disease, when the relation of the symptoms to disease of the adrenals has been fairly well established, it is a question as to how far the symptoms, with the exception of the pigmentation, and possibly of the asthenia, are due to the actual involvement of the adrenal gland. Finally, we must remember that the underlying infection causing the adrenal lesion is in itself capable of causing symptoms sufficiently profound to mask or at least modify any possible symptoms arising from involvement of the adrenal gland.

Nor can we accept, without hesitancy, the *post hoc propter hoc* argument of opotherapy as advocated by many. In the first place, adrenalin is only one of the many products of the internal secretion of the adrenal. Even if we admit that it is the most important of the products, it seems illogical to conclude that the administration of adrenalin will save life when we know that at the same time disease of the equally vital essential cortex coexists. Furthermore, the fallacy of judging the life-saving effects of a drug of such unspecific character as adrenalin in conditions that frequently result in cure by other means are obvious.

It seems to me that the only method whereby we may determine clinical acute (and even chronic) adrenal insufficiency is by means of a physiological test. As adrenalin is the only internal secretion of the organ for which we have fairly approximate tests it is logical to assume that the quantity of adrenalin in the blood is a fair index of adrenal insufficiency, provided, of course, that the medulla of the adrenal is assumed to be involved. The clinical possibilities of carrying out such tests was shown by Whipple.³⁰ Using the physiological test of Elliot and the more accurate chemical test of

³⁰ Jour. Exp. Med., xix, 536.

Folin, Whipple found that in acute experimental intoxications in dogs the adrenal index is low; anesthesia and chloroform poisoning cause a marked drop; in pernicious anemia there is an increase. In acute infections (typhoid, sepsis, peritonitis, etc.) the adrenal index is either normal or slightly below normal. In cases associated with high blood-pressure the index is normal or slightly subnormal.

A more direct method of determining adrenal insufficiency would be by determining the adrenal index direct from the gland itself. This was done in one case by Cooke²¹ in a man acutely ill with delirium and general twitchings. Death occurred two days after the onset. At the autopsy both adrenals were caseous. With the physiological test Cooke found a diminution of adrenalin not only in the diseased areas but also in those portions that appeared normal.

SIDE-LIGHTS ON MULTIPLE MYELOMA.

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I LIKE to observe the old saying, "Let not the cobbler judge above his last," but even a cobbler should, I presume, keep his eyes open. I was prompted also to make this report because pathologists, when doing necropsies, usually can make only a partial examination of the skeleton. Hence there are exceedingly few extended and probably no complete skeletal surveys on multiple myeloma in the literature. Then, too, although pathologists are not agreed upon what is and what is not a myeloma, the series of cases is still small. While reporting a case, MacCallum (1901) also spoke of the still rather limited series of cases. Bombhard (1914) was able to find a series of 54 cases without, however, trying to discriminate between the metastatic and the non-metastatic. Since this series of 54 cases contains a number with metastases to other organs than the bones and cartilages, the actual number of cases of restricted multiple myeloma is undoubtedly considerably smaller. In addition to these 54 cases the references before me would seem to show that 6 more cases were reported in 1914 and two in 1915 and perhaps 1 in 1916.

It is not often that a case of this intensely interesting condition comes to the attention of the anatomist, and when it does he usually

²¹ Arch. Int. Med., 1912, ix, 108.

¹ The anatomical and chemical portions of this paper were written respectively by Meyer and Swain.